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EXAMINER	
GOON, SCARLETT Y	

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Chgpatent@leydig.com

Office Action Summary	Application No.	Applicant(s)	
	10/581,538	DEFREES ET AL.	
	Examiner	Art Unit	
	SCARLETT GOON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *6 and 13-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-12 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20 April 2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to Applicants' Amendment and Remarks filed on 19 April 2010 in which claims 1, 9 and 13 are amended to change the scope and breadth of the claims.

The Declaration of Mr. Shawn DeFrees (inventor), submitted by Applicants on 19 April 2010 under 37 CFR § 1.132, are acknowledged and will be further discussed below.

Claims 1-23 are pending in the instant application.

Claims 6 and 13-22 were previously withdrawn from further consideration in the Office Action dated 17 December 2009 pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and/or nonelected species, there being no allowable generic or linking claim.

Claims 1-5, 7-12 and 23 will be examined on its merits herein.

Information Disclosure Statement

The information disclosure statement (IDS) dated 20 April 2010 complies with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609, except where noted. Accordingly, it has been placed in the application file and the information therein has been considered as to the merits.

Non-patent literature cite no. PK was not considered because a copy of the Kawasaki reference was not provided to the Office.

Specification

Applicants' submission of a paper listing of the sequences cited in the Specification, in the reply filed on 19 April 2010, is acknowledged.

Rejections Withdrawn

Applicants' amendment, filed 19 April 2010, with respect to the rejection of claim 9 under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention, has been fully considered and is persuasive because the claim has been amended to provide a limitation wherein "at least one of r, s, t, and u is 1." This rejection has been **withdrawn**.

Applicants' amendment and remarks, filed 19 April 2010, with respect to the rejection of claims 1, 2, 7, 9, 10, 12 and 23 under 35 U.S.C. 103(a), as being unpatentable over WIPO publication WO 94/05332 to M'Timkulu, in view of U.S. Patent No. 6,586,398 B1 to Kinstler *et al.* and U.S. Patent No. 5,643,575 to Martinez *et al.*, as evidenced by Gervais *et al.*, as evidenced by journal publication to Ulloa-Aguirre *et al.*, and as evidenced by journal publication to Kawasaki *et al.*, have been fully considered and are persuasive because the combined teachings of the prior art do not disclose a conjugate wherein the recited moiety is attached via an intact glycosyl linking group, as recited in the instant claim limitations. This rejection has been **withdrawn**.

Applicants' amendment and remarks, filed 19 April 2010, with respect to the rejection of claims 3-5 under 35 U.S.C. 103(a), as being unpatentable over WIPO

publication WO 94/05332 to M'Timkulu, in view of U.S. Patent No. 6,586,398 B1 to Kinstler *et al.* and U.S. Patent No. 5,643,575 to Martinez *et al.*, as evidenced by Gervais *et al.*, as evidenced by journal publication to Ulloa-Aguirre *et al.*, and as evidenced by journal publication to Kawasaki *et al.*, as applied to claims 1, 2, 7, 9, 10, 12 and 23, further in view of journal publication by Felix *et al.*, have been fully considered and are persuasive because the combined teachings of the prior art do not disclose a conjugate wherein the recited moiety is attached via an intact glycosyl linking group, as recited in the instant claim limitations. This rejection has been **withdrawn**.

Applicants' amendment and remarks, filed 19 April 2010, with respect to the rejection of claims 8 and 11 under 35 U.S.C. 103(a), as being unpatentable over WIPO publication WO 94/05332 to M'Timkulu, in view of U.S. Patent No. 6,586,398 B1 to Kinstler *et al.* and U.S. Patent No. 5,643,575 to Martinez *et al.*, as evidenced by Gervais *et al.*, as evidenced by journal publication to Ulloa-Aguirre *et al.*, and as evidenced by journal publication to Kawasaki *et al.*, as applied to claims 1, 2, 7, 9, 10, 12 and 23, further in view of PG Pub No. US 2003/0166525 A1 to Hoffman *et al.*, have been fully considered and are persuasive because the combined teachings of the prior art do not disclose a conjugate wherein the recited moiety is attached via an intact glycosyl linking group, as recited in the instant claim limitations. This rejection has been **withdrawn**.

Priority

This application is a National Stage entry of PCT/US04/40709 filed on 3 December 2004 and claims priority to U.S. provisional application no. 60/527,082 filed

on 3 December 2003, U.S. provisional application no. 60/539,387 filed on 26 January 2004, U.S. provisional application no. 60/592,744 filed on 29 July 2004, U.S. provisional application no. 60/614,518 filed on 29 September 2004 and U.S. provisional application no. 60/623,387 filed on 29 October 2004.

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir 1994). Also see MPEP § 201.11.

The disclosure of the prior-filed applications, U.S. provisional application no. 60/527,082 filed on 3 December 2003, U.S. provisional application no. 60/539,387 filed on 26 January 2004, and U.S. provisional application no. 60/592,744 filed on 29 July 2004, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The prior filed applications, U.S. provisional application no. 60/527,082 and U.S. provisional application no. 60/539,387, do not disclose a conjugate comprising a branched PEG

comprising serine, cysteine, or lysine. The prior filed applications, U.S. provisional application no. 60/592,744, do not disclose the genus of branched polymers as recited in instant claims 3-5. Specifically, the prior filed application does not disclose varying the carbon chain length, designated as variable "q" in the instant claims.

Thus, the priority date of the instant claims **3-5** is deemed to be the filing date of the earliest application that provides support for the claimed subject matter, that being U.S. provisional application no. 60/614,518 filed on 29 September 2004. If Applicants disagree, Applicants should present a detailed analysis as to why the claimed subject matter has clear support in the earlier priority applications. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

In clarifying the priority date of the instant claims, applicant should note or address whether the art rejections are prior to the priority date of the instant claims and whether said art occurred more than one year prior to said priority date.

Response to Arguments

Applicants have pointed out that U.S. provisional application no. 60/614,518 filed on 29 September 2004 and U.S. provisional application no. 60/623,387 filed on 29 October 2004 provide sufficient support for the subject matter of instant claims 3-5, as shown on p. 28-29 of the Specification of the provisional applications. Thus, the priority date accorded claims 3-5 has been amended as indicated above.

However, it is maintained that U.S. provisional application no. 60/592,744 fails to provide sufficient support for the subject matter of claims 3-5. It is noted that this provisional application provides a generic structure as shown in paragraph [0116] and further indicates that exemplary branched PEGs include a cysteine, serine or di-lysine core in paragraph [0117]. However, although the generic structure of paragraph [0116] indicates that q can represents an integer from 0 to 20, variable B of that structure is not defined to encompass an amide bond, and the branched PEGs of paragraph [0117] do not disclose a variable chain. Thus, U.S. provisional application no. 60/592,744 cannot be considered to provide support for the subject matter of instant claims 3-5.

The following are new ground(s) or modified rejections prompted by Applicants' submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Section [0001]

Claims 1, 2, 7-12 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0605963 A2 to Wright (IDS dated 20 April 2010), in view of PG Pub No. US 2002/0016003 to Saxon *et al.* (IDS dated 20 April 2010), in view of U.S. Patent No. 5,643,575 to Martinez *et al.* (hereinafter referred to as the '575 patent; of record), in view of journal publication by Keene *et al.* (PTO-892, Ref. U), as evidenced by U.S. Patent No. 6,586,398 B1 to Kinstler *et al.* (hereinafter referred to as the '398

patent; of record), as evidenced by Gervais *et al.* (of record), as evidenced by journal publication to Ulloa-Aguirre *et al.* (of record), and as evidenced by journal publication to Kawasaki *et al.* (of record).

Wright teaches methods and compounds for modifying polypeptides with PEG or other water-soluble organic polymers. Protein and other similar organic molecules are chemically modified by covalent conjugation to water-soluble organic polymers, such as PEG, because of the desirable properties conferred on the polypeptides by attachment of the water-soluble polymers. The desirable properties include solubility in aqueous solutions, increased stability during storage, reduced immunogenicity, increased resistance to enzymatic degradation, compatibility with a wider variety of drug administration systems, and increased *in vivo* half-life (p. 2, lines 11-16). Conjugation of mPEG to a cysteine residue of EPO is known (p. 3, lines 5-9). However, Wright teaches that it may be advantageous to couple water-soluble reagents to the carbohydrate moiety of a glycoprotein rather than to the polypeptide backbone amino acids because of differences in charge displacement, steric hinderance, amino acid residues at active sites, and other problems that may disrupt the structure and function of the polypeptide component of the water-soluble polymer modified glycoproteins (p. 3, lines 38-46). By providing for water-soluble polymer reagents that may be coupled to the carbohydrate moiety of glycoproteins it may be possible to covalently conjugate water-soluble polymers to proteins without substantially adversely affecting the biological activity of proteins that would be adversely affected through coupling at other amino acid residues (p. 3, lines 47-50). Wright teaches that hydrazine and oxylamine

derivatives of water-soluble polymers, such as PEG, may be covalently attached to proteins through reactions with aldehyde groups or other suitable functional groups present on the protein of interest (p. 7, lines 5-11). Aldehyde groups may be introduced by partially oxidizing the hydroxyl groups on the polypeptide, such as hydroxyl groups present on the carbohydrate moieties of the polypeptide, with galactose oxidase or periodate (p. 7, lines 11-16). Hydrazide and oxylamine derivatives are further disclosed (p. 7, lines 19-58). Examples of PEG water soluble polymers include polyethylene glycol, methoxypolyethylene glycol, polyethylene glycol homopolymers, polypropylene glycol homopolymers, copolymers of ethylene glycol with propylene glycol (p. 7, line 58 – p. 8, line 3). Wright further teaches that the disclosed preparation may be administered alone or in an admixture with a pharmaceutical carrier or diluent selected with regard to the intended route of administration and standard pharmaceutical practice (p. 12, lines 14-21). Polypeptides of interest for water-soluble polymer derivatization include hormones, lymphokines, cytokines, growth factors, enzymes, vaccine antigens, and antibodies (p. 4, lines 26-29). Methods for the synthesis of mPEG-hydrazide from mPEG-OH (p. 12, line 55 - p. 13, line 37) and mPEG-semicarbazide from mPEG-NH_2 (p. 13, line 50 – p. 14, line 16) are further disclosed. Additionally, methods for the modification of EPO with mPEG-hydrazide and mPEG-semicarbazide are further disclosed wherein EPO is oxidized with sodium periodate followed by conjugation of the resulting aldehyde with PEG (p. 18, line 26 - p. 19, line 14). It is noted that Wright does not expressly teach which carbohydrate group is oxidized to an aldehyde in the presence of sodium periodate. However, as evidenced by Kinstler *et al.*, 10 mM sodium

periodate oxidation of EPO targets the pendant diol of the penultimate glycosyl unit sialic aicd residue (p. 11, lines 1-10 and p. 19, lines 29-33).

The teachings of Wright differ from that of the instantly claimed invention in that Wright does not expressly teach conjugation of the PEG polymer to the 9-position or 5-position of sialic acid, as recited in the instant claims. Furthermore, while Wright discloses that their disclosed conjugation methods are useful for peptide hormones, Wright does not disclose follicle stimulating hormone as one such peptide hormone.

Saxon *et al.* teach a method for covalent modification of molecules. The chemoselective ligation reaction can be carried out under physiological conditions, and involves condensation of a specifically engineered phosphine, which can provide for formation of an amide bond between the two reactive partners resulting in a final product comprising a phosphine oxide, or which can be engineered to comprise a cleavable linker so that a substituent of the phosphine is transferred to the azide of the other molecule (paragraph 0018). The selectivity of the reaction and its compatibility with aqueous environments provides for its application *in vivo* and *in vitro*, e.g. synthesis of peptides and other polymers. Saxon *et al.* disclose the use of a synthetic substrate comprising an abiotic reactive partner, such as the azido compounds of paragraphs 0067-0070, for incorporation into a biopolymer, which is utilized in the glycoprotein biosynthetic pathway. For example, host cells provided with synthetic sialic acid azido-derivatives, such as those disclosed in paragraphs 0067-0070, incorporates these compounds into the sialic acid biosynthetic pathway, eventually resulting in the incorporation and expression of the synthetic sugar residues on glycoproteins

(paragraph 0066). The azido-modified glycoprotein can then undergo a chemoselective ligation reaction with another molecule engineered with a phosphine. The engineered phosphine can be modified to comprise a molecule desired for delivery and conjugation to the azido-target substrate, such as that comprising detectable labels, small molecule drugs, cytotoxic molecules, ligands for binding by a target receptor, tags to aid in purification, and molecules to facilitate selective attachment of the polypeptide to a surface (paragraph 0075). The chemoselective ligation can be performed with a modified phosphine that comprises a cleavable linker. Thus, reaction of i) a first reactant comprising a first molecule of interest engineered with a phosphine comprising a cleavable linker, with ii) a second reactant comprising a second molecule of interest engineered with an azide, results in conjugation of the first molecule of interest to the second molecule of interest via an amide or a thioamide bond, accompanied by the release of nitrogen and an oxidized phosphine byproduct (paragraph 0109). This reaction is further schematically illustrated in paragraph 0109. As shown in Example 6, cells incorporate N-azidoacetylmannosamine into cell surface glycans, as detected by labeling of the cells with biotin modified with a phosphine group, followed by FITC-avidin staining (paragraph 0198). Example 7 illustrates a method wherein two peptides, one modified with an azido group, and the other modified with a phosphine group with a cleavable linker, are conjugated together to form an amide bond between the two peptides. Saxon *et al.* further disclose that previous work showed that incorporation of a ketone-bearing group, such as a levulinoyl group, can be expressed on glycoproteins as SiaLev, wherein the levulinoul group is present at the 5-position of sialic acid, and

that the ketone group on SiaLev can be chemoselectively conjugated to compounds or other molecules bearing a hydrazide group (paragraphs 0008-0010).

The Martinez '575 patent teaches branched, non-antigenic polymers and conjugation of the polymers to biologically active molecules such as proteins and peptides as a means to extend their circulating half-life *in vivo*. One of the chief advantages for the use of branching polymers is that the branching polymers impart an umbrella-like three-dimensional protective covering to the materials they are conjugated with (column 2, lines 42-51). Another advantage is that the branched polymers provide the benefits associated with attaching several strands of polymers to a bioeffecting material, but require substantially fewer conjugation sites, which is apparent in therapeutic agents having few available attachment sites (column 2, lines 52-59). The branched polymers are represented by formula (I), $(R)_nL$-A, wherein R is the water-soluble polymer, n is 2 or 3, L is the aliphatic linking moiety covalently lined to R, and A represents the activating functional group (column 3, lines 11-22). The polymers are preferably prepared from methoxypoly (ethylene glycols), or other suitable alkyl substituted poly(alkylene oxide) derivative, such as those containing mono or bis terminal C_1-C_4 groups (column 2, lines 65 - column 3, line 4). Straight-chained non-antigenic polymers such as monomethyl PEG (mPEG) homopolymers are preferred (column 3, lines 4-6). It is preferred that each mPEG chain have a molecular weight of between 200 and about 12,000 Da, with molecular weights of about 5,000 Da being most preferred (column 3, lines 23-29). The variable L preferably includes a multiply-functionalized alkyl group containing up to 13, and more preferably, between 1-10

carbon atoms (column 3, lines 59-63). A heteroatom, such as nitrogen, oxygen or sulfur may be included within the alkyl chain, which may also be branched at a carbon or nitrogen atom. The variable "A" is selected from any functional group that is capable of reacting with 1) an amino group, 2) a carboxylic acid group or reactive carbonyl group, or 3) mercapto or sulfhydryl groups. The variable "A" can also include a spacer moiety located proximal to the aliphatic linking moiety "L" (column 4, lines 47-50). Biologically active molecules of interest include, but are not limited to, proteins, peptides, polypeptides, enzymes, organic molecules of natural and synthetic origin such as medicinal chemicals, and the like (column 7, lines 40-45). Among the list of proteins cited as being of interest is follicle-stimulating hormone (column 8, line 5). Example 8 discloses the preparation of a branched PEG structure wherein lysine is the linker conjugated to two linear mPEG compounds (column 13, lines 20-40).

Keene *et al.* teach a method for cloning and expression of the β-subunit of human FSH gene in CHO cells. The sequence of the clone is shown in Figure 3 (p. 4772) and is the same as SEQ ID No. 2 of the instant application. Introduction of the clone into Chinese hamster ovary (CHO) cells produces FSH that is biologically active (abstract). As evidenced by Gervais *et al.*, FSH is glycosylated with the same glycosyl structure as shown in instant claim 9 (p. 181, Figure 3A, peak at about 49 min). Additionally, as evidenced by Ulloa-Aguirre *et al.*, human FSH glycosyl modification occurs via N-linked glycosylation to the asparagine residue of the peptide backbone (p. 205, column 2).

As such, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Wright, concerning the modification of peptides, such as hormones, with water-soluble polymers, such as PEG, with the teachings of Saxon *et al.*, regarding chemoselective ligations involving a ketone group with a hydrazide group, or an azido group with a phosphine, with the teachings of the Martinez '575 patent, regarding the conjugation of branched, non-antigenic PEG polymers to biologically active molecules, such as proteins and peptides, e.g. FSH, as a means to extend their circulating half-life *in vivo*, with the teachings of Keene *et al.*, regarding the cloning and expression of the β-subunit of rhFSH in CHO cells. Since Wright teaches that polypeptides, such as hormone, can be conjugated to PEG polymers through the glycosylations present on those peptide molecules, as a means to reduce the immunogenicity of biologically active macromolecules or to increase their *in vivo* half-life, while maintaining their activity, and the Martinez '575 patent teaches that branched, non-antigenic polymers can be conjugated to biologically active molecules, such as FSH, as a means to extend their circulating half-life *in vivo*, it would have been *prima facie* obvious for one of ordinary skill in the art to conjugate PEG to FSH via the glycosylations present on the macromolecules, as described by Wright. Since both Wright and the Martinez '575 patent teach conjugation of PEG to biological macromolecules as a means to extend their serum half-life, and Wright further teaches that hormones can be conjugated using their disclosed method, one of ordinary skill in the art would reasonably expect that the use of follicle stimulating hormone, as disclosed in the Martinez '575 patent, for conjugation to a PEG polymer using the

method disclosed by Wright, would result in PEGylation of FSH at the glycosyl moiety present on FSH.

Furthermore, as Wright teaches that PEG-hydrazide polymers are conjugated to the carbohydrate moiety of biological macromolecules by oxidizing the carbohydrate moiety to an aldehyde or other suitable functional group, one of ordinary skill in the art would have been motivated to conjugate these same PEG-hydrazide derivative, onto the carbohydrate residue of glycoproteins expressing a ketone group, such as that present on SiaLev, as disclosed by Saxon *et al.* Since Saxon *et al.* teach that biotin-hydrazide can be selectively conjugated to the ketone group of SiaLev, which is expressed on the terminus carbohydrate residue of a glycoprotein, one of ordinary skill in the art would reasonably expect that substitution of biotin-hydrazide with PEG-hydrazide would yield a predictable result. One of ordinary skill in the art would consider this to be an advantageous method because it eliminates the need for an oxidation step on a carbohydrate residue.

With regards to obtaining FSH containing a terminal SiaLev group on its glycans, Keene *et al.* teach the expression of rhFSH in a CHO system. Thus, based on the combined teachings of Saxon *et al.* and Keene *et al.*, one of ordinary skill in the art would reasonably expect that expression of FSH in the CHO system in the presence of a mannosamine compound as disclosed by Saxon *et al.*, would predictably yield FSH modified with SiaLev on the terminus of its glycans. Moreover, as Saxon *et al.* teach that azido groups can be introduced onto sialic acids present on glycoproteins using a similar method to that of SiaLev, and that the azido groups chemoselectively react with

phosphine groups, one of ordinary skill in the art would have been motivated to alternately modify the PEG-hydrazide compounds, disclosed by Wright, into PEG-phosphine compounds for conjugation to azido groups introduced onto the sialic acid residue of glycoproteins. One of ordinary skill in the art would have been motivated to select the azide-phosphine chemistry, in order to receive the expected benefit, as disclosed by Saxon *et al.*, that these two groups are abiotic to cell surfaces. One of ordinary skill in the art would have been motivated to conjugate PEG onto FSH, in order to receive the expected benefit, as disclosed by Wright, that conjugation of PEG to a peptide increases its solubility in aqueous solutions, stability during storage, and resistance to enzymatic degradation, and reduces its immunogenicity, as well as increasing its *in vivo* half-life. Moreover, as disclosed by Wright, it may be advantageous to couple PEG to the carbohydrate moiety of a glycoprotein rather than to the polypeptide backbone amino acids because of differences in charge displacement, steric hinderance, amino acid residues at active sites, and other problems that may disrupt the structure and function of the polypeptide component of the water-soluble polymer modified glycoproteins. Thus, although Saxon *et al.* exemplify conjugation of a hydrazide or phosphine group onto sialic acid derivatives expressed on glycoproteins as a detection method, Saxon *et al.* do disclose that small molecules, peptide, ligands, etc., could be conjugated to the azido or ketone group introduced onto sialic acid. As such, in view of the teachings of Wright, it would have been *prima facie* obvious to one of ordinary skill in the art that other molecules could be conjugated to the sialic acid derivatives present on the glycoproteins.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0002]

Claims 3-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0605963 A2 to Wright (IDS dated 20 April 2010), in view of PG Pub No. US 2002/0016003 to Saxon *et al.* (IDS dated 20 April 2010), in view of U.S. Patent No. 5,643,575 to Martinez *et al.* (hereinafter referred to as the '575 patent; of record), in view of journal publication by Keene *et al.* (PTO-892, Ref. U), as evidenced by U.S. Patent No. 6,586,398 B1 to Kinstler *et al.* (hereinafter referred to as the '398 patent; of record), as evidenced by Gervais *et al.* (of record), as evidenced by journal publication to Ulloa-Aguirre *et al.* (of record), and as evidenced by journal publication to Kawasaki *et al.* (of record), as applied to claims 1, 2, 7-12 and 23, further in view of journal publication by Felix *et al.* (of record).

The combined teachings of Wright, Saxon *et al.*, the Martinez '575 patent, and Keene *et al.*, as evidenced by the Kinstler '398 patent, as evidenced by Gervais *et al.*, Ulloa-Aguirre *et al.* and Kawasaki *et al.* were as disclosed in section [0001] above of the claim rejections under 35 USC § 103.

The combined teachings of the prior art differ from that of the instantly claimed invention in that the prior art references do not disclose the specific PEG structures as recited in the instant claims.

Felix *et al.* teach the synthesis of symmetrically and asymmetrically branched pegylating reagents. PEG-protein conjugates have been shown to have improved bioavailability and therapeutic efficacy stemming from increased resistance to proteolytic degradation, enhanced pharmacokinetic and improved pharmacodynamic properties, and reduced renal clearance (p. 86, column 1, first paragraph). Additionally, many pegylated proteins have been reported to have increased plasma half-lives and reduced antigenicity and immunogenicity (p. 86, column 1, first paragraph). Branched PEGs offer an additional dimension of steric protection to the proteins to which they are linked (p. 86, column 2, bridging paragraph). Lysine has been used successfully as a spacer for branched PEG structures (p. 86, column 1, last paragraph). It is expected that introduction of additional branches to PEG would provide additional levels of enzymatic protection to the proteins to which they are linked (p. 86, column 2, first full paragraph). Felix *et al.* disclose a branched bis-pegylating reagent wherein lysine is used as the linker, and a tris-pegylating reagent wherein glutamate-lysine is used as the linker (p. 87, column 1, Figure 1). Methods for the preparation of the bis-pegylating reagent and tris-pegylating reagent are disclosed in Figure 2 (p. 87).

As such, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Wright, concerning the modification of peptides, such as hormones, with water-soluble polymers, such as PEG, with the teachings of Saxon *et al.*, regarding chemoselective ligations involving a ketone group with a hydrazide group, or an azido group with a phosphine, with the teachings of the Martinez '575 patent, regarding the conjugation of branched, non-antigenic PEG

polymers to biologically active molecules, such as proteins and peptides, e.g. FSH, as a means to extend their circulating half-life *in vivo*, with the teachings of Keene *et al.*, regarding the cloning and expression of the β-subunit of rhFSH in CHO cells, with the teachings of Felix *et al.*, regarding a bis-pegylating reagent and a tris-pegylating reagent based on amino acids as the backbone linker.

Since both the Martinez '575 patent and Felix *et al.* teach that one of the chief advantages for the use of branched polymers is that the branching polymers impart an umbrella-like three-dimensional protective covering to the materials they are conjugated with, one of ordinary skill in the art would have been motivated to modify the branched PEG polymers disclosed in the Martinez '575 patent, or by Felix *et al.*, with hydrazide reactive groups, such as that disclosed by Wright, in order to receive the expected benefit that the resulting branched PEGylated FSH would exhibit greater protection with regards to proteolytic cleavage and serum half-life.

Furthermore, since the Martinez '575 patent teaches that branched PEG polymers can be synthesized by using any linker that comprises a multiply-functionalized alkyl group containing up to 13 carbons, further exemplifying lysine as such a linker, and Felix *et al.* teach that lysine and glutamate, individually, or combined, can be used as the linker for generating branched PEG polymers, one of ordinary skill in the art would have been motivated to combine the teachings and arrive at the conclusion that different amino acids could likewise be used as the linker for generation of branched PEG polymers. Since lysine and glutamate are both amino acids, and many of the natural amino acids, such as cysteine and serine, meet the limitations of

being a linker as defined in the Martinez '575 patent, one of ordinary skill in the art would have been motivated to substitute the lysine linker backbone as disclosed in the Martinez '575 patent with other amino acids, such as serine or cysteine, with the expectation that such a substitution would similarly generate useful branched PEG polymers. Moreover, since Felix *et al.* teach that a tris-pegylating reagent can be generated based on a glutamate-lysine backbone, it is would have been *prima facie* obvious for one of ordinary skill to substitute glutamate with another amino acid, such as a lysine residue, to form a lysine-lysine backbone, with the expectation that such a substitution would similarly generate useful tri-branched PEG polymers.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicants' arguments, filed 19 April 2010, with respect to the rejection of claims 1, 2, 7, 9, 10, 12 and 23 under 35 U.S.C. 103(a), as being unpatentable over WIPO publication WO 94/05332 to M'Timkulu, in view of U.S. Patent No. 6,586,398 B1 to Kinstler *et al.* and U.S. Patent No. 5,643,575 to Martinez *et al.*, as evidenced by Gervais *et al.*, as evidenced by journal publication to Ulloa-Aguirre *et al.*, and as evidenced by journal publication to Kawasaki *et al.*, and the rejection of claims 3-5 under 35 USC § 103(a) as being unpatentable over the previously cited references, further in view of journal publication by Felix *et al.*, have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, in view of the references cited

on the IDS filed 20 April 2010, and Applicants' amendment to the claimed limitations, a new ground(s) of rejection is applied, as indicated above. The Declaration of Mr. Shawn DeFrees, submitted by Applicants on 19 April 2010 under 37 CFR § 1.132, is not relevant to this rejection and therefore will not be addressed.

Insofar as Applicants' arguments are still applicable to the instant rejection, Applicants argue that the instant claims are drawn to a conjugate having an "intact glycosyl linking group," which is defined as "a linking group that is derived from a glycosyl moiety in which the individual saccaharide monomer that links the conjugate is not degraded, e.g. oxidized, e.g. by sodium metaperiodate." This argument is not persuasive in view of the new grounds of rejections applied above. Specifically, Saxon *et al.* disclose the introduction of ketones or azides onto a glysoside residue of a glycoconjugate present on a peptide or protein via the cell's metabolic pathway. Additionally, Wright teaches that PEG hydrazide derivatives could be conjugated to aldehydes or other suitable functional groups present on the glycoside of a peptide backbone. Thus, it would have been *prima facie* obvious to conjugate the PEG hydrazide derivatives of Wright to the ketone moiety presented on cell surface glycoconjugates via the method of Saxon *et al.*, as discussed in the rejection above. The instantly claimed invention is *prima facie* obvious over the combined teachings of the prior art, as discussed in the rejection above.

The following rejections of record in the previous Office Action are maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Section [0003]

Claims 1, 2, 7-12 and 23 are rejected under 35 U.S.C. 102(a) and 35 U.S.C. 102(e) as being anticipated by WIPO publication WO 03/031464 A2 to DeFrees *et al.* (please see PG Pub No. US 2007/0042458 A1 for equivalent; of record), as evidenced by journal publication by Ulloa-Aguirre *et al.* (of record), and as evidenced by PG Pub No. US 2003/0166525 A1 to Hoffman *et al.* (of record).

DeFrees *et al.* disclose methods and compositions for remodeling a peptide molecule, including the addition or deletion of one or more glycosyl groups to the peptide, and/or the addition of a modifying group to the peptide. Modifying groups include water-soluble polymers, such as poly(ethylene glycol) (p. 152, lines 7-25 of WIPO; paragraphs 0655-0657 of PG Pub). The use of poly(ethylene glycol) to derivatize peptide therapeutics has been demonstrated to reduce the immunogenicity of the peptides and prolong their clearance time from circulation (paragraph 0011 of PG Pub). The PEG moiety has been shown to be attached via a peptide amino acid

residue (paragraph 0013 of PG Pub) or an oxidized glycosyl residue of the peptide (paragraph 0014 of PG Pub). DeFrees *et al.* disclose an *in vitro* method for the modification of erythropoietin (EPO), wherein the peptide has the formula –AA-X^1-X^2 (paragraph 0031 of PG Pub) or formula –AA-$(X^1)_n$. More specific structures of the X^1-X^2 glycosyl residues are shown in paragraph [0067], paragraph [0082], paragraph [0088], paragraph [0090] and paragraph [0114]. Scheme 3 discloses a modified glycoPEG-ylated compound, such as albumin-PEG-SA-EPO, wherein EPO represents erythropoietin and SA represents sialic acid, which can be used in a method for extending the blood-circulation half-life of selected peptide (p. 149, Scheme 3 and lines 1-10 of WIPO; paragraph 0643 of PG Pub). Additionally, Example 23 discloses a method for glycoPEGylation of human pituitary-derived follicle stimulating hormone (FSH) (paragraphs 1567-1573) and Example 24 discloses a method for the glycoPEGylation of recombinant FSH produced recombinantly in CHO cells (paragraphs 1574-1579). The methods are further schematically represented in Figure 34 which discloses the modification of the glycan structure on follicle stimulating hormone with PEG (paragraph 0219 of PG Pub). The modifying group can be attached to sialic acid occurs at either the 9-position on the pyruvyl side chain or at the 5-position on the amine moiety of sialic acid (p. 150, lines 5-11 of WIPO; paragraph 0647 of PG Pub). DeFrees *et al.* further teach that the reactive functional groups between the sugar moiety and the modifying group can include such functional groups as amines and carboxyl groups (paragraphs 0753. 0754, and 0760 of PG Pub).

It is noted that DeFrees *et al.* do not expressly disclose the site of glycoPEGylation on the peptide backbone, or the sequence FSH. However, as evidenced by Hoffmann *et al.*, human FSH has the sequence as disclosed in Seq. ID No. 5 and Seq. ID No. 6 (columns 39 and 40), corresponding to the α- and β-subunits, respectively. Applicants are requested to note that their instantly claimed SEQ ID No. 1 and 2 are non-compliant as the sequences were not submitted with the application. In the absence of any additional information provided in the Specification with regards to the specific sequences of SEQ ID No. 1 and 2 as recited in claim 8, SEQ ID No. 1 and 2 is considered to have the same sequence as Seq. ID No. 5 and 6, respectively, as disclosed by Hoffmann *et al.* Therefore, since DeFrees *et al.* teach that the FSH used in their method was derived from a human, it is expected that it would have the same sequence as that disclosed by Hoffmann *et al.* With regards to the site of glycosylation, as evidenced by Ulloa-Aguirre *et al.*, N-glycosylation of FSH occurs at positions N52 and N78 of the α-subunit, and at positions N7 and N24 of the β-subunit. Therefore, it is inherent that the PEGylated glycosyl residue would be present only at these four asparagine sites.

Thus, the disclosure of a glycoPEGylated FSH, as well as a method for the preparation of said structure, disclosed by DeFrees *et al.*, anticipates claims 1, 2, 7-12 and 23.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Section [0004]

Claims 3-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO publication WO 03/031464 A2 to DeFrees *et al.* (please see PG Pub No. US 2007/0042458 A1 for equivalent; of record), as evidenced by journal publication by Ulloa-Aguirre *et al.* (of record), and as evidenced by PG Pub No. US 2003/0166525 A1 to Hoffman *et al.* (of record), as applied to claims 1, 2, 7-12 and 23, further in view of U.S. Patent No. 5,643,575 to Martinez *et al.* (hereinafter referred to as the '575 patent; of record) and journal publication by Felix *et al.* (of record).

The teachings of DeFrees *et al.* were as disclosed in section [0003] above of the claim rejections made under 35 USC § 102. The evidentiary disclosure of Gervais *et al.*, Ulloa-Aguirre *et al.*, and Hoffman *et al.*, were as disclosed above in the claim rejections made under 35 USC § 102.

The teachings of DeFrees *et al.* differ from that of the instantly claimed invention in that DeFrees *et al.* do not expressly teach PEG moieties having the structures as recited in the instant claims.

The Martinez '575 patent teaches branched, non-antigenic polymers and conjugation of the polymers to biologically active molecules such as proteins and

peptides as a means to extend their circulating half-life *in vivo*. One of the chief advantages for the use of branching polymers is that the branching polymers impart an umbrella-like three-dimensional protective covering to the materials they are conjugated with (column 2, lines 42-51). Another advantage is that the branched polymers provide the benefits associated with attaching several strands of polymers to a bioeffecting material, but require substantially fewer conjugation sites, which is apparent in therapeutic agents having few available attachment sites (column 2, lines 52-59). The branched polymers are represented by formula (I), $(R)_nL$-A, wherein R is the water-soluble polymer, n is 2 or 3, L is the aliphatic linking moiety covalently lined to R, and A represents the activating functional group (column 3, lines 11-22). The polymers are preferably prepared from methoxypoly (ethylene glycols), or other suitable alkyl substituted poly(alkylene oxide) derivative, such as those containing mono or bis terminal C_1-C_4 groups (column 2, lines 65 - column 3, line 4). Straight-chained non-antigenic polymers such as monomethyl PEG (mPEG) homopolymers are preferred (column 3, lines 4-6). It is preferred that each mPEG chain have a molecular weight of between 200 and about 12,000 Da, with molecular weights of about 5,000 Da being most preferred (column 3, lines 23-29). The variable L preferably includes a multiply-functionalized alkyl group containing up to 13, and more preferably, between 1-10 carbon atoms (column 3, lines 59-63). A heteroatom, such as nitrogen, oxygen or sulfur may be included within the alkyl chain, which may also be branched at a carbon or nitrogen atom. The variable "A" is selected from any functional group that is capable of reacting with 1) an amino group, 2) a carboxylic acid group or reactive carbonyl group,

or 3) mercapto or sulfhydryl groups. The variable "A" can also include a spacer moiety located proximal to the aliphatic linking moiety "L" (column 4, lines 47-50). Biologically active molecules of interest include, but are not limited to, proteins, peptides, polypeptides, enzymes, organic molecules of natural and synthetic origin such as medicinal chemicals, and the like (column 7, lines 40-45). Among the list of proteins cited as being of interest is follicle-stimulating hormone (column 8, line 5). Example 8 discloses the preparation of a branched PEG structure wherein lysine is the linker conjugated to two linear mPEG compounds (column 13, lines 20-40).

Felix *et al.* teach the synthesis of symmetrically and asymmetrically branched pegylating reagents. PEG-protein conjugates have been shown to have improved bioavailability and therapeutic efficacy stemming from increased resistance to proteolytic degradation, enhanced pharmacokinetic and improved pharmacodynamic properties, and reduced renal clearance (p. 86, column 1, first paragraph). Additionally, many pegylated proteins have been reported to have increased plasma half-lives and reduced antigenicity and immunogenicity (p. 86, column 1, first paragraph). Branched PEGS offer an additional dimension of steric protection to the proteins to which they are linked (p. 86, column 2, bridging paragraph). Lysine has been used successfully as a spacer for branched PEG structures (p. 86, column 1, last paragraph). It is expected that introduction of additional branches to PEG would provide additional levels of enzymatic protection to the proteins to which they are linked (p. 86, column 2, first full paragraph). Felix *et al.* disclose a branched bis-pegylating reagent wherein lysine is used as the linker, and a tris-pegylating reagent wherein glutamate-lysine is used as the

linker (p. 87, column 1, Figure 1). Methods for the preparation of the bis-pegylating reagent and tris-pegylating reagent are disclosed in Figure 2 (p. 87).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of DeFrees *et al.*, concerning a glycoPEGylated FSH, with the teachings of the Martinez '575 patent, regarding the use of branched, non-antigenic PEG polymers and conjugation of these PEG polymers to biologically active molecules such as proteins and peptides as a means to extend their circulating half-life *in vivo*, with the teachings of Felix *et al.*, regarding a bis-pegylating reagent and a tris-pegylating reagent based on amino acids, such as lysine and glutamate-lysine, as the backbone linker. Since both the Martinez '575 patent and Felix *et al.* teach that one of the chief advantages for the use of branched polymers is that the branching polymers impart an umbrella-like three-dimensional protective covering to the materials they are conjugated with, one of ordinary skill in the art would have been motivated to substitute the linear PEG polymers of PEGylated FSH with the branched polymers disclosed in either the Martinez '575 patent or by Felix *et al.*, in order to receive the expected benefit that the resulting branched PEGylated FSH would exhibit greater protection with regards to proteolytic cleavage and serum half-life.

Furthermore, since the Martinez '575 patent teaches that branched PEG polymers can be synthesized by using any linker that comprises a multiply-functionalized alkyl group containing up to 13 carbons, further exemplifying lysine as such a linker, and Felix *et al.* teach that lysine and glutamate, individually, or combined, can be used as the linker for generating branched PEG polymers, one of ordinary skill in

the art would have been motivated to combine the teachings and arrive at the conclusion that different amino acids could likewise be used as the linker for generation of branched PEG polymers. Since lysine and glutamate are both amino acids, and many of the natural amino acids, such as cysteine and serine, meet the limitations of being a linker as defined in the Martinez '575 patent, one of ordinary skill in the art would have been motivated to substitute the lysine linker backbone as disclosed in the Martinez '575 patent with other amino acids, such as serine or cysteine, with the expectation that such a substitution would similarly generate useful branched PEG polymers. Moreover, since Felix *et al.* teach that a tris-pegylating reagent can be generated based on a glutamate-lysine backbone, it would have been *prima facie* obvious for one of ordinary skill to substitute glutamate with another amino acid, such as a lysine residue, to form a lysine-lysine backbone, with the expectation that such a substitution would similarly generate useful tri-branched PEG polymers.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicants' arguments, filed 19 April 2010 and the Declaration of Mr. Shawn DeFrees, submitted on 19 April 2010 under 37 CFR § 1.132, with respect to the rejection of claims 1, 2, 7-12 and 23 made under 35 USC § 102(a) and 102(e) as being anticipated by WIPO publication WO 03/031464 A2 to DeFrees *et al.*, as evidenced by journal publication by Ulloa-Aguirre *et al.*, and as evidenced by PG Pub No. US

2003/0166525 A1 to Hoffman *et al.*, and the rejection of claims 3-5 made under 35 USC § 103(a) as being unpatentable over the previously cited references, further in view of U.S. Patent No. 5,643,575 to Martinez *et al.* and journal publication by Felix *et al.*, have been fully considered but they are not persuasive.

Applicants argue that they have submitted a Declaration under 37 C.F.R. § 1.132 to state that the cited portions of the presently claimed invention disclosed but not claimed in the DeFrees PCT Publication were invented by them or derived from them (i.e., DeFrees, Baer, and/or Bowe), and thus, the DeFrees PCT Publication is not "to another," as required under 35 USC § 102(e). Applicant's arguments and the Declaration of Mr. DeFrees have been carefully reviewed but are not considered persuasive.

The Declaration of Mr. DeFrees states that the cited "portion of International Patent Application Publication WO 2003/031464 describes subject matter invented by me or derived from my work." This statement is insufficient to overcome the applied 102(e) rejection. Applicants are referred to MPEP § 715.01(b) and § 715.01(c). Specifically, in addition to stating that the subject matter of the WIPO application was invented by one or derived from one's work, the Declaration must also clearly state who was the first person to invent the cited portions of the claimed invention in the WIPO application. Additionally, to avoid a new 35 USC § 103(a) rejection, Applicants are requested to provide a statement showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Furthermore, Applicants are requested to note that the WIPO publication was also applied under a 35 USC § 102(a) rejection. This rejection was not addressed by Applicants. The requirements to be stated in a Declaration to overcome a rejection applied under 35 USC § 102(a) is different from that applied under 35 USC § 102(e). To overcome the rejection applied under 35 USC § 102(a), Applicants are again referred to MPEP § 715.01(c).

In order to overcome the instant 35 USC § 103(a), Applicants are requested to note that this rejection might be overcome by a statement : (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The rejections are still deemed proper and therefore maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 10 and 23 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12, 18 and 19 of copending U.S. application no. 12/418,530, in view of U.S. Patent No. 6,586,398 B1 to Kinstler *et al.* (hereinafter referred to as the '398 patent; of record).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a method of making a composition comprising a first polypeptide conjugate, wherein said first polypeptide conjugate comprises a first number of poly(alkylene oxide) moieties covalently linked to said first polypeptide. The poly(alkylene oxide) moieties are linked to the polypeptide via an O-linked or N-linked glycan residue. Claim 9 indicates that the poly(alkylene oxide) moieties is selected from the group consisting of poly(ethylene glycol) or poly(propylene glycol). Claim 12 indicates that the peptide may be selected from a group that includes follicle stimulating hormone. Claim 19 indicates that the glycosyl linking moiety may be selected from a group that includes sialic acid.

The claims of the instant application are drawn to a follicle stimulating hormone peptide conjugate comprising at least one moiety having the formula as shown in instant claim 1. Claims 3-5 further limit the modifying group present on the conjugate to branched PEG polymers as recited in said claims.

The copending application does not expressly disclose that the site of conjugation of PEG onto the sialic acid residue. The Kinstler '398 patent teaches that water-soluble polymers, such as PEG, can be linked to a hyperglycosylated erythropoietin analog (NESP) by various methods, one of which involves the mild oxidation of NESP under conditions selected to target the pendant diol of the penultimate glycosyl unit sialic acid for oxidation to an aldehyde (column 5, lines 25-32). The resultant glycoaldehyde is then reacted with the water-soluble polymer, such as a PEG compound.

Thus, based on the teachings of the Kinstler '398 patent, one of ordinary skill in the art would have been motivated to attach PEG to the pendant diol position of the sialic residue of the FSH peptide disclosed in copending U.S. application no. 12/418,530, with the expectation that such a conjugation reaction would result in the desired conjugate.

Thus, the instant claims 1, 10 and 23 are seen to be obvious over claims 1-12, 18 and 19 of copending U.S. application no. 12/418,530, in view of U.S. Patent No. 6,586,398 B1 to Kinstler *et al.*

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 1 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2 and 12 of copending U.S. application no. 12/152,587, in view of U.S. Patent No. 6,586,398 B1 to Kinstler *et al.* (hereinafter referred to as the '398 patent; of record).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a polypeptide conjugate comprising the structure as shown in formula (I). Claim 2 indicates that the peptide may be follicle stimulating hormone. Claim 12 indicates that the polymeric moiety is poly(ethylene glycol).

The claims of the instant application are drawn to a follicle stimulating hormone peptide conjugate comprising at least one moiety having the formula as shown in instant claim 1. Claims 3-5 further limit the modifying group present on the conjugate to branched PEG polymers as recited in said claims.

The copending application does not expressly disclose that the glycosyl moiety of the peptide for conjugation of the polymeric moiety is a sialic acid residue. The Kinstler '398 patent teaches that water-soluble polymers, such as PEG, can be linked to a hyperglycosylated erythropoietin analog (NESP) by various methods, one of which involves the mild oxidation of NESP under conditions selected to target the pendant diol of the penultimate glycosyl unit sialic acid for oxidation to an aldehyde (column 5, lines 25-32). The resultant glycoaldehyde is then reacted with the water-soluble polymer, such as a PEG compound.

Thus, based on the teachings of the Kinstler '398 patent, one of ordinary skill in the art would have been motivated to attach PEG to the sialic residue of the FSH peptide disclosed in copending U.S. application no. 12/152,587, with the expectation that such a conjugation reaction would result in the desired conjugate.

Thus, the instant claim 1 is seen to be obvious over claims 1, 2 and 12 of copending U.S. application no. 12/152,587, in view of U.S. Patent No. 6,586,398 B1 to Kinstler *et al.*

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 1 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 10, 16, 19 and 21 of copending U.S. application no. 11/781,885.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a polypeptide conjugate comprising the structure as shown in formula (V). Claim 19 indicates that the peptide may be selected from a group that includes follicle stimulating hormone. Claim 16 indicates that the polymeric moiety is poly(ethylene glycol). Claim 21 indicates that the polymeric moiety is attached via the sugar residue denoted as formula (VII).

The claims of the instant application are drawn to a follicle stimulating hormone peptide conjugate comprising at least one moiety having the formula as shown in instant

claim 1. Claims 3-5 further limit the modifying group present on the conjugate to branched PEG polymers as recited in said claims.

Thus, the instant claim 1 is seen to be obvious over claims 10, 16, 19 and 21 of copending U.S. application no. 11/781,885.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 1 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13, 20, 23 and 26 of copending U.S. application no. 11/781,900.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a polypeptide conjugate comprising the structure as shown in formula (V). Claim 23 indicates that the peptide may be selected from a group that includes follicle stimulating hormone. Claim 20 indicates that the polymeric moiety is poly(ethylene glycol). Claim 26 indicates that the polymeric moiety is attached via the sugar residue denoted as formula (VII).

The claims of the instant application are drawn to a follicle stimulating hormone peptide conjugate comprising at least one moiety having the formula as shown in instant claim 1. Claims 3-5 further limit the modifying group present on the conjugate to branched PEG polymers as recited in said claims.

Thus, the instant claim 1 is seen to be obvious over claims 13, 20, 23 and 26 of copending U.S. application no. 11/781,900.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1 and 3 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3, 5, 6, 10, 15, 16, 19, 21 and 22 of copending U.S. application no. 11/781,888.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a generic polypeptide conjugate as defined in claim 1, as well as a polypeptide conjugate comprising the structure as shown in formula (V). Claims 6 and 19 indicate that the peptide may be selected from a group that includes follicle stimulating hormone. Claims 3, 5 and 16 indicate that the polymeric moiety is poly(ethylene glycol) that is linear or branched, with structures as defined in said claims. Claims 5 and 21 indicate that the polymeric moiety is attached via the sugar residue denoted as formulas (III) or (VII).

The claims of the instant application are drawn to a follicle stimulating hormone peptide conjugate comprising at least one moiety having the formula as shown in instant claim 1. Claims 3-5 further limit the modifying group present on the conjugate to branched PEG polymers as recited in said claims.

Thus, the instant claims 1 and 3 are seen to be obvious over claims 1, 3, 5, 6, 10, 15, 16, 19, 21 and 22 of copending U.S. application no. 11/781,888.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 1 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 27, 32, 38 and 39 of copending U.S. application no. 11/866,969, in view of U.S. Patent No. 6,586,398 B1 to Kinstler *et al.* (hereinafter referred to as the '398 patent; of record).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a method of isolating a first polypeptide conjugate comprising a first number of PEG moieties covalently linked to said first polypeptide, from a second polypeptide conjugate comprising a second number of PEG moieties covalently linked to said second polypeptide. Claim 32 indicates that the peptide may be selected from a group that includes follicle stimulating hormone. Claims 38 and 39 indicate that the PEG moiety is attached to the polypeptide via a glycosyl linking group.

The claims of the instant application are drawn to a follicle stimulating hormone peptide conjugate comprising at least one moiety having the formula as shown in instant claim 1. Claims 3-5 further limit the modifying group present on the conjugate to branched PEG polymers as recited in said claims.

The copending application does not expressly disclose that the glycosyl moiety of the peptide for conjugation of the polymeric moiety is a sialic acid residue. The Kinstler '398 patent teaches that water-soluble polymers, such as PEG, can be linked to a hyperglycosylated erythropoietin analog (NESP) by various methods, one of which involves the mild oxidation of NESP under conditions selected to target the pendant diol

of the penultimate glycosyl unit sialic acid for oxidation to an aldehyde (column 5, lines 25-32). The resultant glycoaldehyde is then reacted with the water-soluble polymer, such as a PEG compound.

Thus, based on the teachings of the Kinstler '398 patent, one of ordinary skill in the art would have been motivated to attach PEG to the sialic residue of the FSH peptide disclosed in copending U.S. application no. 11/866,969, with the expectation that such a conjugation reaction would result in the desired conjugate.

Thus, the instant claim 1 is seen to be obvious over claims 27, 32, 38 and 39 of copending U.S. application no. 11/866,969, view of U.S. Patent No. 6,586,398 B1 to Kinstler *et al.*

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 3 and 23 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8, 10, 23 and 26-28 of copending U.S. application no. 11/781,896.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a generic polypeptide conjugate as defined in claim 1. Claims 8 and 23 indicate that the peptide may be selected from a group that includes follicle stimulating hormone. Claims 3, 4, 7 and 27 indicate that the polymeric moiety is poly(ethylene glycol) that is linear or branched, with

structures as defined in said claims. Claims 7 and 26 indicate that the polymeric moiety is attached via the sugar residue denoted as formulas (III) or (VII).

The claims of the instant application are drawn to a follicle stimulating hormone peptide conjugate comprising at least one moiety having the formula as shown in instant claim 1. Claims 3-5 further limit the modifying group present on the conjugate to branched PEG polymers as recited in said claims.

Thus, the instant claims 1, 3 and 23 are seen to be obvious over claims 1-8, 10, 23 and 26-28 of copending U.S. application no. 11/781,896.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 3 and 23 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8, 10, 23 and 26-28 of copending U.S. application no. 11/781,902.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a generic polypeptide conjugate as defined in claim 1. Claims 8 and 23 indicate that the peptide may be selected from a group that includes follicle stimulating hormone. Claims 3, 4, 7 and 27 indicate that the polymeric moiety is poly(ethylene glycol) that is linear or branched, with structures as defined in said claims. Claims 7 and 26 indicate that the polymeric moiety is attached via the sugar residue denoted as formulas (III) or (VII).

The claims of the instant application are drawn to a follicle stimulating hormone peptide conjugate comprising at least one moiety having the formula as shown in instant claim 1. Claims 3-5 further limit the modifying group present on the conjugate to branched PEG polymers as recited in said claims.

Thus, the instant claims 1, 3 and 23 are seen to be obvious over claims 1-8, 10, 23 and 26-28 of copending U.S. application no. 11/781,902.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1 and 23 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 89-136 of copending U.S. application no. 11/714,874.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to an O-linked covalent conjugate of a peptide having the formulas as defined in claims 89, 103, 110 or 115. Claim 125 indicates that the peptide may be selected from a group that includes follicle stimulating hormone. Claims 122-124 indicate that the polymeric moiety is poly(ethylene glycol). Claim 112 indicates that the glycosyl linking group is sialic acid. Claim 133 defines the structure of sialic acid modified with the polymeric modifying group PEG.

The claims of the instant application are drawn to a follicle stimulating hormone peptide conjugate comprising at least one moiety having the formula as shown in instant

claim 1. Claims 3-5 further limit the modifying group present on the conjugate to branched PEG polymers as recited in said claims.

Thus, the instant claims 1 and 23 are seen to be obvious over claims 89-136 of copending U.S. application no. 11/714,874.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1 and 23 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-43 of U.S. Patent No. 7,473,680 B2.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent is drawn to a method of forming a covalent conjugate between a water soluble polymer and a glycosylated or non-glycosylated peptide. Claims 41 and 43 indicate that the peptide may be selected from a group that includes follicle stimulating hormone. Claims 5-8, 21-23 and 42 indicate that the polymeric moiety is poly(ethylene glycol). Claim 42 further indicates that PEG is conjugated to the glycosyl linking group sialic acid at C-5. Claim 133 defines the structure of sialic acid modified with the polymeric modifying group PEG.

The claims of the instant application are drawn to a follicle stimulating hormone peptide conjugate comprising at least one moiety having the formula as shown in instant claim 1. Claims 3-5 further limit the modifying group present on the conjugate to branched PEG polymers as recited in said claims.

Thus, the instant claims 1 and 23 are seen to be anticipated by claims 1-43 of U.S. Patent No. 7,473,680 B2.

Claims 1, 7, 9 and 23 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-120 of U.S. Patent No. 7,416,858 B2.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent is drawn to a pharmaceutical composition comprising a pharmaceutically acceptable diluent and a covalent conjugate between PEG and a glycosylated or non-glycosylated peptide, wherein said PEG is conjugated to said peptide via a glycosyl linking group, wherein said glycosyl linking group is interposed between and covalently linked to both said peptide and said PEG. Claims 9, 23 and 40, for example, indicate that the peptide may be selected from a group that includes follicle stimulating hormone. Claim 112 indicates that the modified glycosyl moiety, and the glycosyl moiety linking PEG to the peptide, has the structure as in said claim. PEG is conjugated to the glycosyl linking group sialic acid at C-5. Claim 133 defines the structure of sialic acid modified with the polymeric modifying group PEG.

The claims of the instant application are drawn to a follicle stimulating hormone peptide conjugate comprising at least one moiety having the formula as shown in instant claim 1. Claims 3-5 further limit the modifying group present on the conjugate to branched PEG polymers as recited in said claims. Claim 9 further limits the glycosyl moiety of the peptide.

Thus, the instant claims 1, 7, 9 and 23 are seen to be anticipated by claims 1-120 of U.S. Patent No. 7,416,858 B2.

Claims 1, 7 and 23 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 7,138,371 B2.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent is drawn to a covalent conjugate between PEG and a peptide, wherein said PEG is covalently attached to said peptide at a glycosyl or amino acid residue of said peptide via an intact glycosyl linking group comprising a sialic acid residue covalently linked to said PEG. Claims 14, 19 and 25 indicate that the peptide may be selected from a group that includes follicle stimulating hormone. Claims 11, 17 and 24, for example, indicate at which position PEG is conjugated to sialic acid.

The claims of the instant application are drawn to a follicle stimulating hormone peptide conjugate comprising at least one moiety having the formula as shown in instant claim 1. Claims 3-5 further limit the modifying group present on the conjugate to branched PEG polymers as recited in said claims. Claim 9 further limits the glycosyl moiety of the peptide.

Thus, the instant claims 1, 7 and 23 are seen to be anticipated by claims 1-27 of U.S. Patent No. 7,138,371 B2.

Response to Arguments

Applicants' intent that the obviousness-type double-patenting rejections over the copending applications cited above be held in abeyance until the present claims are otherwise found to be allowable, in the reply filed on 19 April 2010, is acknowledged.

Applicants' indication that a terminal disclaimer will be filed to overcome the obviousness-type double-patenting rejections over the U.S. Patents cited above upon determination that one or more claims in the present application is otherwise allowable, in the reply filed on 19 April 2010, is acknowledged.

The rejections are still deemed proper and therefore maintained.

Conclusion

In view of the rejections to the pending claims set forth above, no claim is allowed.

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 20 April 2010 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner
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